REMARKS

Interview

The undersigned appreciates the time the Examiner took to have an interview concerning this application and appreciates the suggestions made by the Examiner during the interview.

Comments Regarding the Amendment Filed 27 April 2001

An Amendment After Final was filed on 27 April 2001 but was not entered. Consequently the present Amendment After Final is drafted in a manner such that the 27 April 2001 amendments to the claims do not exist and the changes are based on the claims as they stood after entry of the Amendment filed 25 October 2000.

Rejections Under 35 U.S.C. § 112, second paragraph

The Advisory Action stated that claims 2 and 4 as amended by the Amendment After Final filed 27 April 2001 were indefinite. Those amendments were never entered. The present amendments do not result in any changes to claims 2 and 4 which therefore remain in their original form as filed. The non-amended claims 2 and 4 have never been rejected as being indefinite.

Rejections Under 35 U.S.C. § 103

Claims 1-4 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sechler et al. in view of Wydner et al. Claims 1-4 are drawn to a mouse or mouse cell comprising i) exactly one functional elastin gene or ii) a mouse or mouse cell comprising no elastin gene. In brief, the rejection is that the Sechler et al. reference teaches making transgenic mice which are +/- or -/- for a rat tropoelastin gene. The Wydner et al. reference teaches the sequence of the mouse elastin gene.

Applicants urge that at best the combination of the cited references would motivate one of skill in the art to make mice which are transgenic for a **mutated** mouse elastin gene but which also comprise normal wild-type mouse elastin genes. The mice of the Sechler et al. reference comprise not only the transgenic mutant rat elastin gene but also comprise the normal wild-type mouse elastin genes which are still active. This is seen in several places in the reference. The first paragraph of

the Results and discussion section on page 150 of the Sechler et al. reference states that the reasoning behind the construction of the mice was to produce mice which would synthesize a mutated elastin which would be incorporated into the elastin matrix together with the normal, endogenous mouse elastin. This clearly establishes the motivation of producing the mice - to study animals making a combination of both mutant and wild-type elastin. Data showing that the mice studied for the publication did in fact produce both types of elastin is shown, e.g., in Table 1 on page 153 of the Sechler et al. publication. Both rat and mouse tropoelastin mRNA were produced with the levels of endogenous mouse tropoelastin mRNA set at a value of 100% and the rat levels based on a comparison to that value. The middle of the last paragraph on page 14 of the publication states that levels of expression of the rat transgenes in skin was usually comparable to or exceeded that of the endogenous expression of the mouse gene. Table 2 on page 158 of the Sechler et al. publication shows that both the rat and mouse elastin proteins were being synthesized in the transgenic animals.

The claims which are pending are not drawn to mice or mouse cells comprising a **mutated** gene plus a wild-type gene, rather the claims are drawn to mice or cells which have a) a single functional elastin gene or ii) no elastin gene. This difference is critical. The claimed mice and cells are ones which end up being **deficient** in elastin rather than comprising some type of **mutated** elastin. Mice (and humans) which are deficient in elastin have different medical conditions than those which synthesize a mutated elastin.

Claims 1 and 3 have been amended to state that the "nonfunctional elastin gene" as it had previously been referred to means a gene which comprises a null mutation. The "nonfunctional" language is no longer present in the claim, but the requirement for a null mutation is now present in those cases in which a second elastin gene is present. The amended claims therefore do not encompass elastin genes which are transcribed but are nonfunctional because of a mutation which is present, rather they encompass the presence of only at most a single elastin gene which produces an elastin protein which can be incorporated into a matrix. Support for a "null mutation" is found throughout the application, e.g., page 2, lines 17-18, and on page 5, lines 9-24. It is urged that this amended claim language more clearly distinguishes the claims from the prior art and prevents the claims from being read broadly enough to be encompassed by or made obvious by the prior art. No

prior art reference has been cited which teaches a mouse or mouse cell which comprises zero or only one elastin gene which will be transcribed into RNA which will be translated into a protein which can be incorporated into the extracellular matrix.

The Advisory Action mailed 16 May 2001 stated that the rejection was being maintained despite the above arguments which were submitted in the Amendment After Final filed 27 April 2001. Applicants urge that the Office Actions continue to overlook a crucial difference between the prior art and the claimed invention. The prior art teaches medical problems which are associated with the presence of a **mutated** elastin, not with a **deficiency** of elastin. The Sechler et al. reference teaches on pages 162-163 that disruptions in the region of the elastin gene are associated with SVAS. In fact, this teaching states that it was not known if the disruption of the elastin gene causes the SVAS phenotype or whether the defect results from a disruption of another gene near the elastin gene (see the final sentence on page 162 continuing onto page 163). Based on this fact alone, it is urged that at best there would be merely an "obvious to try" motivation to produce mice with mutated elastin genes and the usefulness of such mice would not be "obvious". This alone should be enough to overcome the "obviousness" rejection. However, applicants urge that there are even more reasons that the obviousness rejection is improper. If one were to accept that the references teach that mutations in elastin actually do result in SVAS, the Sechler et al. reference teaches that these mutations involve a breakpoint near the 3' end of the tropoelastin gene (see the final paragraph on page 162). This means that a somewhat truncated version of elastin is produced and it is this truncated version which causes SVAS. The Sechler et al. reference teaches that there is support for the idea that incorporation of the truncated elastin into fibers results in SVAS (see page 163). Therefore to study SVAS one would be motivated to produce **mutated** elastin such that a mutant form of elastin would be produced and be inserted into fibers to produce aberrant fibers. That is exactly what Sechler et al. did and that is what their results support, i.e., they prepared mice which produced mutated forms of elastin. Sechler et al. produced no mice which were deficient in elastin, rather their mice produced normal amounts of wild-type elastin plus a mutated form of elastin which interacted with wild-type elastin in forming aberrant fibers and produced mice which have fiber morphology similar to SVAS (see page 163). These results would point one in the direction of

studying mutated forms of elastin rather than gene dosage effects. It is urged that no references have been pointed to which disclose any studies on mice which are deficient in elastin, rather the prior art teaches that conditions such as SVAS are likely caused by mutated forms of elastin being incorporated into fibers thereby producing aberrant fibers. This would not lead one to conclude that a mouse producing a deficient amount of solely wild-type elastin would produce aberrant fibers since only wild-type elastin would be present. The results disclosed in the present application teach otherwise, but such studies were never reported in the prior art. The medical condition which results from a lack of elastin is different from that seen due to the presence of a mutated elastin. Mutated elastin leads to aberrant elastic fibers whereas a lack of elastin results in proliferation of smooth muscle and contributes to obstructive arterial disease (see Summary of the Invention on pages 2-3 of the application). It is urged that the prior art would lead one only to study mice with mutated forms of elastin, not to study mice with solely a deficiency of wild-type elastin.

Claims 5, 6, 9 and 10 were rejected as being unpatentable over Reitamo et al. in view of Sechler et al. and Wydner et al. These claims are drawn to methods for screening for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis.

First it is urged that claim 6 was improperly included in this rejection. In the first Office Action which was mailed 2 February 2000, claim 6 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Maruyama et al. in view of Sechler whereas claims 5, 9 and 10 were rejected as being unpatentable over Reitamo et al. in view of Li et al., Su et al. and Li et al. Claim 6 differs from claim 5, 9 and 10 in that it concerns a method of measuring elastase activity whereas the other claims are not concerned with elastase activity. It was the Maruyama et al. reference which was cited for its teaching of elastase. The presently cited Reitamo et al., Sechler et al. and Wydner et al. references do not include a teaching of elastase and it is urged that they cannot make obvious a method which requires the use of elastase.

The Advisory Action maintained that claim 6 is obvious in view of the prior art despite the above arguments. It is urged that claim 6 must be viewed separately from claims 5, 9 and 10 which were part of the same rejection. Claim 6 is drawn to a method which requires the measurement of

elastase. The prior art which has been cited does not even teach the existence of elastase. It is urged that at a minimum, for prior art to make a claim obvious it must show that all elements of a claim were known or obvious. Because the cited references do not even mention elastase and do not teach the function of elastase, it is not understood how those references, standing alone, can make obvious the invention claimed by claim 6. Furthermore, Applicants do not understand the reasoning set forth in the Advisory Action. The Advisory Action seems to state that the prior art teaches upregulating elastin gene expression and measuring the effect of a compound on the expression of an elastin gene. This is followed by stating that this makes obvious that one of skill in the art would measure the effect of a compound on elastase. The connection to elastase is not seen. Elastase activity is not the activity of elastin. Elastase is an enzyme that degrades elastin. Elastase and elastin are totally distinct proteins. The Advisory Action has out of thin air pulled in a reference to elastase with no support for making such a statement.

Claims 5, 9 and 10 are hereby amended to refer to mice or humans or their cells which are *ELN* +/- with the further requirement that these organisms or cells comprise only one functional elastin gene and either no second elastin gene or an elastin gene with a null mutation. It is urged that these amendments prevent the claims from being read to encompass the use of organisms or cells which comprise one wild-type elastin gene plus one mutated elastin gene wherein the mutated elastin gene results in the synthesis of a mutated elastin which can be incorporated into extracellular matrix. It is urged that the cited prior art neither teaches nor suggests a mouse or human with only a single elastin gene which produces elastin which will be incorporated into extracellular matrix or using such organisms or cells for drug screening for drugs which will be useful for treating atherosclerosis, SVAS or hypertension. The arguments set forth above concerning the fact that the prior art would lead one only to study animals with mutated versions of elastin and not animals which are deficient in elastin apply to claims 5, 9 and 10 which require the use of animals which are deficient in elastin.

In view of the amendments and above arguments, it is requested that the rejections under 35 U.S.C. § 103(a) be withdrawn.

In view of the amendments and above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application. Together with this Amendment, Applicants have paid for a further extension of time to cover a second month of extension. If any further extensions of time are required, the Examiner is authorized to charge such extension of time to our deposit account number 02-2135.

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Attachments: Marked-Up Copy of Amendments to Claims 1, 3, 5, 9 and 10.

Amended Claims: Version with markings to show changes made

1 (three times amended). A mouse comprising a genome comprising a) exactly one functional elastin gene and b) either one [nonfunctional] mouse elastin gene comprising a null mutation or no second elastin gene.

3 (three times amended). A mouse cell comprising a genome comprising a) exactly one functional elastin gene and b) one [nonfunctional] mouse elastin gene comprising a null mutation or no second elastin gene.

5 (twice amended). A method to screen for drug candidates useful for treating humans with SVAS, hypertension or atherosclerosis or useful for preventing atherosclerosis in humans, said method comprising administering said drugs to an *ELN* +/- mouse or human, wherein said *ELN* +/- mouse or human comprises a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, wherein drugs which inhibit occlusion of arteries in said organism are said drug candidates.

9 (twice amended). A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating an *ELN* +/- mouse or human or *ELN* +/- mouse or human cells, wherein said *ELN* +/- mouse or human or mouse or human cells comprise a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, with drugs and measuring synthesis of elastin RNA wherein a drug which increases synthesis of elastin RNA in said organisms or in said cells is said drug candidate.

10 (amended). A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating *ELN* +/- mice or *ELN* +/- mouse cells, wherein said *ELN* +/- mice or mouse cells comprise a genome with a) exactly one functional elastin gene and b) either one elastin gene comprising a null mutation or no second elastin gene, with drugs and measuring synthesis of elastin wherein a drug which increases synthesis of elastin is said drug candidate.